REMARKS

Claims 1-10 are pending in the application. This amendment is made to correct typographical errors and to further clarify the Applicants invention. Support for the amendment can be found throughout the specification as filed. For example, see page 8, lines 10 - 13. No new matter is introduced by this amendment.

The Invention.

The present invention provides fusion polypeptides comprising a signal peptide functional in *Aspergillus*, a secreted polypeptide or portion thereof normally secreted from *Aspergillus*, an optional cleavable linker and a desired glycosyltransferase from which the transmembrane anchor region has been deleted.

Status of the Application.

Claims 11-18 are pending in the application.

35 U.S.C. §103.

The Examiner has maintained his rejection of Claims 11-18 under 35 USC §103(a) as being unpatentable over either Lawlis (a) *et al.* (US Pat. No. 5,679,543) or Lawlis (b) *et al.* (US Pat. No. 6,130,063) and Kitagawa *et al.* (BBRC (1994) 194(1):375-382). Applicants respectfully traverse the rejections.

Applicants will address each of these references in turn, starting with the common reference, Kitagawa *et al.*

Kitagawa et al. (BBRC (1994) 194(1):375-382)

Kitagawa *et al.* does not teach or suggest: 1) a secretion signal functional in *Aspergillus*; 2) a secreted polypeptide or portion thereof which is normally secreted from a filamentous fungus, and particularly from *Aspergillus*; or 3) optionally a cleavable linker polypeptide. *Kitagawa et al. fails to provide a fusion protein as currently claimed.*

Kitagawa *et al.* uses a mammalian insulin secretion signal (i.e., dog; see Quesenberry, M. S. and Drickamer, K. (1991) Glycobiology 1, 615–621) and a protein A IgG binding domain linked to the glycosyltransferase. Protein A is not a secreted protein even from its native host; it is a membrane bound protein. Furthermore, the protein A isn't for enhancing the expression and secretion of the heterologous protein; it is for ease in purification. There is no teaching that the mammalian secretion signal would be functional in *Aspergillus*. Nor does Kitagawa *et al.* provide for an optional cleavable linker; there is no cleavable linker. Furthermore, *it is well known in the art*

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that one cannot transfer the expression/secretion results from one host to another with a reasonable expectation of success.

Applicants therefore submit that the Kitagawa *et al.* disclosure is limited in three significant areas: 1) it fails to teach a secretion signal functional in *Aspergillus*; 2) it fails to provide an amino acid sequence comprising a secreted polypeptide or portion thereof normally secreted from *Aspergillus;* and 3) an optional cleavable linker sequence.

Lawlis et al. (a) (US Pat. No. 5,679,543) or Lawlis et al. (b) (US Pat. No. 6,130,063)

Lawlis *et al.* (a or b) teaches that heterologous proteins may be secreted at enhanced levels as fusion proteins compared to the levels achieved when it is not fused to a secreted *Aspergillus* polypeptide; there is no teaching that enhanced expression and secretion of a normally membrane-bound protein compared to mammalian expression systems can be achieved. Lawlis *et al.* (a or b) also teaches the stable expression of heterologous proteins via integration of the plasmids. See column 16, lines 59 et seq. However, Lawlis *et al.* (a or b) fails to describe a fusion polypeptide that is encompassed by the presently amended claims. It fails to teach or suggest that: 1) a normally membrane-bound enzyme such as a glycosyltransferase can be secreted, and 2) a truncated gene is suitable for expression in an integration plasmid.

The Examiner argues that Lawlis *et al.* (a or b) teaches that "the second portion of the fusion protein comprises an amino acid sequence of a secreted polypeptide *or a portion thereof* normally secreted from *Aspergillus*." See page 5 of the Office Action, emphasis in original. However, this misapplies Lawlis (a or b). The second portion may be truncated not the desired polypeptide which is the fourth portion. *Thus, the Examiner's assertion that Lawlis et al. (a or b) teaches a major portion of the instant invention is incorrect.*

Moreover, Lawlis *et al.* (a or b) enumerates numerous full-length proteins in its general description and it exemplifies only one protein, chymosin, which is a full-length protease. Contrary to the Examiner's assertion, Lawlis *et al.* (a or b) fails to teach or suggest that a truncated gene or a gene encoding a membrane-bound protein is compatible with the DNA construct contemplated therein. Lawlis *et al.* (a or b) enumerates "bovine chymosin, human tissue plasminogen activator etc., mammalian hormones such as human growth hormone, human interferon, human interleukin and mammalian proteins such as human serum albumin. Desired polypeptides also induce bacterial enzymes such as α-amylase from Bacillus species, lipase from Pseudomonas species, etc. Desired polypeptides further include fungal enzymes such as lignin peroxidase and Mn^{2+}-dependent peroxidase from Phanerochaete, glucoamylase from Humicola species and aspartyl proteases from Mucor species" – all full-length proteins! Not a single membrane-bound or truncated protein is disclosed, suggested or taught. The skilled artisan would not, upon reading

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Lawlis *et al.* (a or b), conclude that membrane-bound or truncated proteins were contemplated therein.

Furthermore, there is no teaching in Lawlis *et al.* (a or b) that a truncated version of the desired protein would result in a functional protein being expressed and secreted when fused to a secreted protein native to *Aspergillus*. Linking the truncated protein to another protein may result in an incorrectly folded protein or a protein that is subject to incorrect/improper processing. Truncation, while it may work in other expression systems, was not taught or suggested in Lawlis *et al.* (a or b).

The claimed combination is not obvious

A *prima facie* case of obviousness requires the Examiner to cite to a reference or a combination of references which (a) suggests or motivates one of skill in the art to modify the teachings of the reference(s) to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims at issue. *See e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness as discussed below.

A. There is no reasonable expectation of success

The reasonable expectation of success must be founded in the prior art, not Applicant's disclosure, and in view of the prior art's lack of correlation between mammalian and fungal expression systems, no logical argument can be advanced in support of the cited reference's teaching of a reasonable expectation of success based on either Lawlis (a) *et al.* (US Pat. No. 5,679,543) or Lawlis (b) *et al.* (US Pat. No. 6,130,063) and Kitagawa *et al.* (BBRC (1994) 194(1):375-382). Certainly there is no motivation to combine the references as suggested by the Examiner or by the references themselves. The modification failed to possess the requisite expectation of success.

Under patent law with regard to obviousness, a reasonable expectation of success is to be assessed from the perspective of one of ordinary skill in the art at the time the invention was made. At the time the invention was made it was well established that not only were there differences in the expression and secretion levels of various constructs within a single host

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organism but also that similar constructs give different results in different organisms. *Thus one skilled in the art would not have a reasonable expectation of success in transferring one expression construct from one host system to another OR that using the insulin secretion signal or protein A would effect secretion of a glycosyltransferase.*

It is axiomatic that a claimed invention is not obvious solely because it is composed of elements that are all individually found in the prior art. See, e.g., *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2D (BNA) 1453, 1457 (Fed. Cir. 1998). Thus, even though Kitagawa *et al.* teaches that a sialyltransferase may be transiently expressed in mammalian cells as a truncated form it does not render obvious the presently claimed invention. For the Kitagawa *et al.* article to render the presently claimed invention obvious, there must have been, at the time the invention was made, a reasonable expectation of success in applying Kitagawa *et al.*'s teachings. See *Micro Chem., Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2D (BNA) 1238, 1245 (Fed. Cir. 1997); *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2D (BNA) 1673, 1681 (Fed. Cir. 1988). Because the Kitagawa *et al.* reference teaches a transient expression system in mammalian cells there was no reason a person skilled in the art would have had a reasonable expectation of success that using this mammalian expression construct would have been successful in a fungal system.

Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. See *Micro Chem.*, 103 F.3d at 1547, 41 U.S.P.Q.2D (BNA) at 1245. The skilled artisan recognizes, even today, that one cannot move from one expression system to another without a concern of failure.

That Applicants were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. See *Standard Oil*, 774 F.2d at 454, 227 U.S.P.Q. (BNA) at 297. Applicants assert that a finding to the contrary relies on the impermissible use of hindsight–using the inventors' success as evidence that the success would have been expected. See *In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2D (BNA) 1313, 1316 (Fed. Cir. 2000) (noting the importance of casting the mind back to the time of the invention to avoid the "insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher").

B. At best, there is an obvious to try situation. This is not a proper standard of review.

An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *See generally In re*

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O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (defining obvious-to-try as when prior art gives "only general guidance as to the particular form of the claimed invention or how to achieve it").

The present case presents a classic "obvious-to-try" situation. Lawlis *et al.* (a) and/or (b) provide teachings that normally extracellular proteins may be expressed in a filamentous fungal host using a specific expression construct. There is no guidance on whether a truncated form of a normally cell-bound protein would be secreted or that it would fold correctly and retain activity.

Furthermore, although Kitagawa *et al.* was able to get secretion in a mammalian system there is a teaching in the reference that goes against what is taught by Lawlis *et al.* (a or b)! Specifically, Lawlis *et al.* (a or b) requires a normally secreted protein be used whereas Kitagawa *et al.* uses a protein, protein A, which is not a secreted protein. Similiarly, Kitagawa *et al.* and Lawlis *et al.* (a or b) differ on the need for a cleavable linker. *Thus, there is a conflict in the teachings of the two references.*

Applicant believes that, at best, the Examiner presents an "obvious to try" standard in determining the patentability of the present invention, a standard which has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 (Fed. Cir. 1989). Thus, Applicant respectfully requests that this rejection be withdrawn and the Claims be passed to allowance.

C. There is no motivation to combine the references as suggested by the Examiner.

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the references to arrive at the **claimed invention**. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

None of the references contain a suggestion or teaching that they should be combined in a way that results in the present invention. In fact, as noted elsewhere herein, there are numerous teachings away from the present invention.

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The Examiner asserts that Lawlis *et al.* (a or b) teaches the "production of any protein irrespective of the fact whether it is normally bound or not." Applicants respectfully disagree. Lawlis *et al.* (a or b) teaches that the desired polypeptides "include mammalian enzymes such as bovine chymosin, human tissue plasminogen activator etc., mammalian hormones such as human growth hormone, human interferon, human interleukin and mammalian proteins such as human serum albumin. Desired polypeptides also include bacterial enzymes such as α-amylase from Bacillus species, lipase from Pseudomonas species, etc. Desired polypeptides further include fungal enzymes such as lignin peroxidase and Mn^{2+}-dependent peroxidase from Phanerochaete, glucoamylase from Humicola species and aspartyl proteases from Mucor species." It should be noted that these are all intact, mature secreted proteins and that Lawlis *et al.* (a or b) particularly describes the production of chymosin, an full-length extracellular protease. There is NO mention that truncated proteins will work in the system. Thus, Lawlis *et al.* (a or b) fails to suggest that a truncated protein would be a "desired polypeptide."

With respect to Kitagawa *et al.*, the Examiner asserts that this reference teaches "the cloning and expression of a polynucleotide encoding a human sialyltransferase lacking the signal-anchor (i.e., membrane anchor) sequences (the first 60 amino acids) as [a] fusion protein comprising the human insulin signal sequence in the place of the signal-anchor peptide in the instant invention and comprising protein A in place of the secreted Aspergillus polypeptide in the instant invention." The Examiner further asserts that "sialyltransferase as a soluble protein" is provided by the Kitagawa *et al.* reference. Although this may be correct the Examiner has ignored the fact that the transfer of an expression cassette useful in one host system is not transferable to another, different, host system. There is no teaching in Kitagawa *et al.* that the truncated gene if fused to another protein or fragment thereof with yet another different signal sequence in yet another host system that it would function properly. As noted above, not only are there differences in the expression and secretion levels of various constructs within a single host organism but also that similar constructs give different results in different organisms. Thus, *not only is there NO motivation to combine Kitagawa et al. with either Lawlis et al. (a or b) there is actually a reason NOT to combine the references as stated by the Examiner.* It is just as likely, if not more so, that the only reason there was secretion of an active enzyme is due to the presence of the protein A in the construct and that without that sequence then proper folding of the enzyme would not have occurred. In other words, there is no reason to believe that the truncated sialyltransferase would possess activity if fused to another protein. In addition, there is no reason why a skilled artisan would use the truncated gene without the other elements of the mammalian expression construct for use in a fungal expression construct. The Examiner's assertions simply are conjecture and a matter of opinion without the necessary support for a finding of obviousness.

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Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

The Commissioner is hereby authorized to charge the fees necessitated by the filing of these documents, or to charge any additional fees under 37 C.F.R. 1.16 and 1.17, or to credit any overpayment, to Deposit Account No. 07-1048.

Date: July 21, 2004

Respectfully submitted,

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